

Review

Extra-nodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: A systematic review and an exploratory meta-analysis



A. Nottegar<sup>a</sup>, N. Veronese<sup>b</sup>, M. Senthil<sup>c</sup>, R.M. Roumen<sup>d</sup>,  
B. Stubbs<sup>e</sup>, A.H. Choi<sup>c</sup>, N.C. Verheuve<sup>f</sup>, M. Solmi<sup>g</sup>, A. Pea<sup>h</sup>,  
P. Capelli<sup>a</sup>, M. Fassan<sup>b</sup>, G. Sergi<sup>b</sup>, E. Manzato<sup>b</sup>, M. Maruzzo<sup>i</sup>,  
F. Bagante<sup>h</sup>, M. Koç<sup>j</sup>, M.A. Eryilmaz<sup>k</sup>, E. Bria<sup>l</sup>, L. Carbognin<sup>l</sup>,  
F. Bonetti<sup>a</sup>, M. Barbareschi<sup>m</sup>, C. Luchini<sup>a,m,n,\*</sup>

<sup>a</sup> Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona, Italy

<sup>b</sup> Department of Medicine, DIMED, University of Padua, Padua, Italy

<sup>c</sup> Department of Surgery, Loma Linda University, Loma Linda, CA, USA

<sup>d</sup> Department of Medical Oncology, School for Oncology and Developmental Biology (GROW), Maastricht University Medical Center, Maastricht, The Netherlands

<sup>e</sup> Health Service and Population Research Department, King's College London, De Crespigny Park, London, UK

<sup>f</sup> Department of Surgery, Máxima Medical Center, Veldhoven, The Netherlands

<sup>g</sup> Department of Neuroscience, University of Padua, Padua, Italy

<sup>h</sup> Department of Surgery, University and Hospital Trust of Verona, Verona, Italy

<sup>i</sup> Medical Oncology Unit, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto IOV-IRCCS, Padova, Italy

<sup>j</sup> Necmettin Erbakan University, Meram Medical School Department of Radiation Oncology, Konya, Turkey

<sup>k</sup> Health Science University, Konya Training and Educational Hospital, Department of General Surgery, Konya, Turkey

<sup>l</sup> Medical Oncology, University and Hospital Trust of Verona, Verona, Italy

<sup>m</sup> Department of Pathology, Santa Chiara Hospital, Trento, Italy

<sup>n</sup> ARC-NET Research Center, University and Hospital Trust of Verona, Verona, Italy

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Abstract

Invasive breast cancer is the most common malignancy in women. Its most common site of metastasis is represented by the lymph nodes of axilla, and the sentinel lymph node (SLN) is the first station of nodal metastasis. Axillary SLN biopsy accurately predicts axillary lymph node status and has been accepted as standard of care for nodal staging in breast cancer. To date, the morphologic aspects of SLN metastasis have not been considered by the oncologic staging system. Extranodal extension (ENE) of nodal metastasis, defined as extension of neoplastic cells through the nodal capsule into the peri-nodal adipose tissue, has recently emerged as an important prognostic factor in several types of malignancies. It has also been considered as a possible predictor of non-sentinel node tumor burden in SLN-positive breast cancer patients. We sought out to clarify the prognostic role of ENE in SLN-positive breast cancer patients in terms of overall and disease-free survival by conducting a systematic review and meta-analysis. Among 172 screened articles, 5 were eligible for the meta-analysis; they globally include 624 patients (163 ENE+ and 461 ENE–) with a median follow-up of 58 months. ENE was associated with a higher risk of

\* Corresponding author. Department of Diagnostics and Public Health University and Hospital Trust of Verona, Piazzale Scuro, 10, 37134 Verona, Italy. Tel.: +39 (0)45 812 4842; fax: +39 (0)45 812 7136.

E-mail addresses: [claudio.luchini@katamail.com](mailto:claudio.luchini@katamail.com), [claudio.luchini@univr.it](mailto:claudio.luchini@univr.it) (C. Luchini).

both mortality (RR = 2.51; 95% CI: 1.66–3.79,  $p < 0.0001$ ,  $I^2 = 0\%$ ) and recurrence of disease (RR = 2.07, 95% CI: 1.38–3.10,  $p < 0.0001$ ,  $I^2 = 0\%$ ). These findings recommend the consideration of ENE from the gross sampling to the histopathological evaluation, in perspectives to be validated and included in the oncologic staging.

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## Introduction

Invasive breast cancer is the most common malignancy in women, representing 23% of all cancers in woman globally and 27% in affluent countries. It is more than twice as common as cancer at any other site.<sup>1</sup> The most common site of metastasis of breast cancer is represented by the lymph nodes of axilla, and the sentinel lymph node (SLN) is the first station of nodal metastasis.<sup>1–3</sup>

Axillary SLN biopsy was introduced in the management of patients affected by T1 and T2 breast cancer and has become the standard care for these patients, being an accurate method in predicting other axillary lymph nodes status.<sup>2,3</sup> The probability of non-SLN metastases in patients with SLN free of metastases is less than 5%. For this reason, such patients can safely avoid axillary lymph node dissection and the associated morbidity.<sup>2–6</sup> Patients with positive SLN were traditionally treated with axillary lymph node dissection.<sup>5,6</sup> However, about 40–60% of these patients have no other metastatic axillary lymph nodes, suggesting that even this group is heterogeneous.

Several factors have been studied as potential predictors of the status of axillary lymph nodes in patients with positive SLN, and some of them have not demonstrated a prognostic value. For example, the presence of isolated tumor cells in the SLN does not adversely impact disease free- and overall-survival, and, according to the Tumor, Nodes, Metastasis (TNM) staging system, isolated tumor cells are designated and treated as pN0(i+).<sup>7</sup> At the same time, extranodal extension (ENE) has recently emerged as an important prognostic factor in several types of malignancies.<sup>8–11</sup> It is the extension of neoplastic cells through the nodal capsule into the peri-nodal adipose tissue (Fig. 1). In positive SLN, ENE has been indicated as a possible predictor of non-SLN tumor burden in breast cancer, but it is yet unclear if ENE in SLN has a significant prognostic impact.<sup>12</sup>

In order to study in depth the prognostic role of ENE in positive SLN of breast cancer patients, we conducted a systematic review and meta-analysis of all the studies that have investigated the most important prognostic indicators, including overall survival (OS), disease-free survival (DFS) and cancer-specific survival, in patients with (ENE+) versus without (ENE–) ENE in SLN.

## Materials and methods

This systematic review adhered to the MOOSE guidelines<sup>13</sup> and PRISMA statement,<sup>14</sup> following a predetermined but unpublished protocol.

### Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they satisfy the following criteria: 1) diagnosis of breast cancer, 2) prospective, observational cohort studies, 3) contained a comparison of prognostic factors between ENE+ vs. ENE– for SLN, 4) contained data about mortality or recurrence of disease, 5) were published in a peer review journal or published abstract. Exclusion criteria were: 1) no presence of cancer, 2) no data about prognostic parameters in the title/abstract, 3) comparison between ENE+ vs. no lymph nodes metastases (N0), 4) diagnosis of non-epithelial malignancies (i.e.: lymphomas), 5) ENE+ for lymph nodes other than SLN, and 6) in vitro or animal studies. We considered articles written in any language.

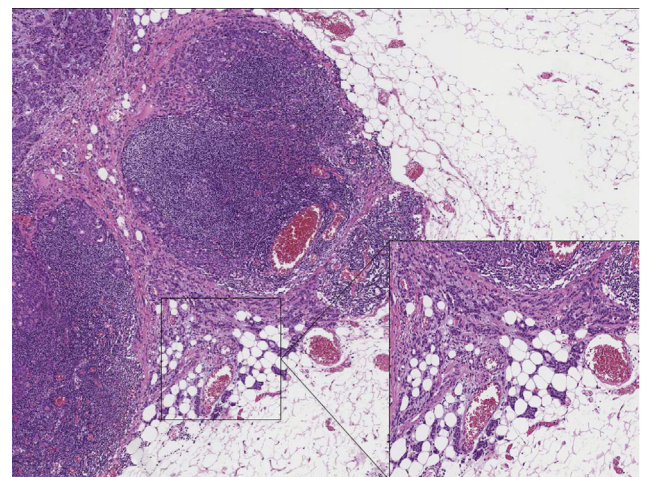


Figure 1. A classical example of extra-nodal extension of nodal metastasis is here shown. The metastatic tumor is a breast carcinoma of non-special type. Note the rupture of nodal capsule and the invasion by the metastatic cells of the peri-nodal adipose tissue. (Original magnification: 4× lymph node, 10× detail in the box).

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